IS ATHEROSCLEROSIS A PEDIATRIC DISEASE?

Don P. Wilson, M.D., FNLA. Diplomate, American Board of Clinical Lipidology, Endowed Chair, Pediatric Cardiovascular Health and Risk Prevention, Pediatric Endocrinology and Diabetes. Cook Children's Medical Center, Fort Worth, Texas. don.wilson@cookchildrens.org

Updated January 21, 2023

ABSTRACT

In the US and other developed countries, cardiovascular disease is a major health burden and the leading cause of death. There are at least three lines of evidence that support the concept of atherosclerosis, the principle cause of cardiovascular disease, having its origins in childhood. Although the most direct is in children with genetic dyslipidemia, such as familial hypercholesterolemia, there is evidence that in-utero and acquired effects may play a role as well. The ability to identify genetic mutations and/or acquired factors or conditions early in childhood creates the opportunity to prevent development of risk factors and future CVD-related events by effective and timely intervention.

INTRODUCTION

Since publication of the National Cholesterol Education Program (NCEP) recommendations in 1992 (1), there has been growing interest in early identification and intervention of children at moderate to high risk of premature cardiovascular disease. Since that time, additional pediatric specific guidelines and recommendations have been published (2,3, 4). A fundamental question, however, is whether atherosclerosis, the underlying basis for cardiovascular disease, is a pediatric disease.

Arteriosclerosis is characterized by deposits of lipoproteins and calcium in the arterial intima (plaques), resulting in inflammation and subsequent fibrosis. The buildup of arterial plaques reduces blood flow and often leads to symptoms of cardiovascular disease (CVD), such as angina, and CVD-related events, such as myocardial infarction and stroke. Although the atherosclerotic process rarely leads to CVD-related symptoms or events in children, its origins can be demonstrated at a very young age in those with genetic mutations and acquired risk factors and conditions. In contrast to those with heterozygous familial hypercholesterolemia, children with a homozygous disease have early clinical manifestations (xanthoma) and significant, symptomatic ASCVD that generally results in premature death, often during adolescence or early adulthood.

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FETAL STUDIES

During pregnancy maternal hypercholesterolemia, such as occurs in women with familial hypercholesterolemia, may have an adverse effect on the future health of the fetus. The presence of greatly increased fatty streak formation in human fetal arteries has been reported in over 50% of fetuses of mothers who were hypercholesterolemic during pregnancy (5). Strong correlations were noted between maternal and fetal plasma cholesterol levels, which in turn were proportional to the extent of lesion formation in the fetus. Despite similar plasma cholesterol levels during childhood, atherosclerosis in children of hypercholesterolemic mothers progressed much more rapidly than did children of mothers who had normal cholesterol levels (6). Use of cholesterol lowering agents or antioxidants in the mother greatly reduced fetal and postnatal atherosclerosis in the offspring (7).

A potential mechanism for this susceptibility to atherosclerosis is suggested by animal models that demonstrate persistence differences in arterial gene expression after birth between offspring of mothers who have normal compared to elevated levels of cholesterol. This evidence supports the assumption that fetal lesion information is associated with genetic programming, which may in turn affect postnatal atherogenesis (8). Cholesterol-lowering and antioxidant treatment during pregnancy appear to positively influence in-utero programming and decrease postnatal susceptibility to atherogenesis (9).

OBSERVATIONAL/EPIDEMIOLOGIC STUDIES

Fatty streaks, the earliest progenitor lesions, are present from early childhood and well established by 20 or 30 years of age. Such lesions, as well as raised plaques, increase rapidly in prevalence and extent during the 15-34 year age span. Relatively advanced levels of atherosclerosis, including fibrous plaques, have been found in adolescents and young adults. (10-12). Fatty streaks progress to raised lesions at vulnerable anatomic sites (13). Vascular surfaces subjected to turbulent flow, the preferred sites for fatty streaks, are the same sites as those for advanced lesions, the latter being vulnerable to plaque rupture and thrombosis (10,14,15). Observational studies from autopsies have helped inform us about the timing, extent and severity of atherosclerotic lesions. Thirty percent (30%) of autopsy specimens of black males contained aortic atheroma by age 10 years (16). Autopsy studies of U.S. soldiers killed during the Korean War showed significant evidence of CVD in 77% of soldiers, with an average age of 22 years. (17). Similar findings were reported in Vietnam War casualties (18).

In addition to autopsy findings, studies using noninvasive measures, including carotid intima-medial thickness (cIMT) and arterial distensibility, have shown anatomic and functional changes of atherosclerosis in youth (10-23). Thickness of the far wall of the internal carotid progresses with age and risk factors alone and together predict thickness in young adults (24).

The risk factors associated with early arterial lesions in children and young adults are the same as those associated with the advanced lesions that cause symptomatic coronary artery disease in adulthood (12, 25). Increased body mass index (BMI), systolic and diastolic blood pressures, and low-density lipoprotein cholesterol (LDL-C), low levels of high density lipoprotein cholesterol (HDL-C), diabetes mellitus, and the presence of cigarette smoking are all associated with greater atherosclerotic plaque coverage and more advanced atherosclerotic lesions. (12,26-28). Autopsy data show that the severity of asymptomatic CVD increases as the number of risk factors increase from 2 - 39 years of age (13,29).

Based on considerable evidence, we can conclude that observational and epidemiologic studies have documented: 1) the origins of atherosclerosis are present from a very early age; 2) there is a striking increase in both the severity and extent of atherosclerosis as age and the number of risk factors increase; 3) the presence and intensity of risk factors are highly correlated with the extent and severity of atherosclerosis; and 4) the combined impact of multiple risk factors is exponentially greater than individual factors alone.

MENDELIAN RANDOMIZATION STUDIES

Genetic mutations characterized by lifelong elevations of cholesterol are associated with increased cardiovascular disease and premature events, and provide the best evidence relating risk to future probability of ASCVD. Conversely, genome wide analysis has demonstrated many alleles that profoundly decrease CVD risk by lifelong lower levels of cholesterol (Table 1). (30-32). It cannot be assumed, however, that a comparable level of lipid lowering achieved with the use of medication will offer the same protective effects (33). This, in part, may be due to initiation of lipid-lowering therapy after clinical disease is recognized, which may be insufficient to prevent the progression of established atherosclerosis. Additionally, the duration of the low cholesterol level is lifelong vs. relatively short number of years on lipid lowering therapy.

In a 20-year follow-up study of statin therapy in children with hypercholesterolemia, 98% of whom had genetically confirmed FH, early treatment was shown to slow the progression of cIMT thickness and reduced the risk of CVD in adulthood (34). In this study of 184 subjects with FH were compared to 77 unaffected siblings, as well as the outcomes of their affected parent. The mean LDL-C level in the subjects with FH decreased 32% from the baseline (237.3 to 160.7 mg/L or 6.13 to 4.16 mmol/L); while treatment goals of LDL-C <100 mg/dL (2.59 mmol/L) were achieved in only 20%. Mean progression of cIMT thickness was not significantly different between those with FH and their siblings, indicating a normalization of the rate of cIMT thickening. The cumulative incidence of CVD-related events (1% vs. 26%) and of death from CVD causes at 39 years of age (0% vs. 7%) was lower among the subjects with FH than among their affected parents. Such findings suggest early identification and initiation of effective lipid lowering therapy, although not to LDL-C levels less than 100 mg/dL, significantly reduces the occurrence and progression of atherosclerosis.

Thus, growing trial evidence is consistent with genetic studies that support therapeutic intervention to achieve lower lipid levels, although the long-term safely and efficacy of medications to accomplish this goal in the pediatric population cannot be documented at this time.

Table 1. Key Mendelian Randomization Studies				
Mutation	**LDL-Cholesterol Reduction**			**CHD Risk**
APOC-III (35)	↓16%	↓23.4 mg/dL	(0.60 mmol/L)	↓40%
NPC1L1 (36)	---	↓12 mg/dL	(0.31 mmol/L)	↓53%
PCSK9 (30)				
Blacks	↓28%	↓40 mg/dL	(1.0 mmol/L)	↓88%
Whites	↓15%	↓20 mg/dL	(0.5 mmol/L)	↓47%
From: Wilson, Don P and Gidding, S. The Journal of Clinical Lipidology. September–October, 2015. Volume 9, Issue 5, Supplement, Pages S1–S4				

Although limited information is available in youth, there is growing interest in the role of TGs as a CVD risk factor. Mendelian randomization studies of individuals with TG-lowering variants in the lipoprotein lipase gene and LDL-C-lowering variants in the LDL receptor gene were found to be associated with similar lower risk of coronary heart disease per 10-mg/dL lower level of ApoB-containing lipoproteins (odds ratios of 0.771 and 0.773, respectively). Importantly, the clinical benefit of lower TG levels was similar to that of lower LDL-C levels per 10mg/dl decrease in ApoB. However, a much larger decrease in TG levels (approx. 70mg/dl) was required to decrease Apo B by 10mg compared to LDL cholesterol (approx. 14mg/dl). This finding suggests that the causal effect of all ApoB-containing lipoprotein particles on the risk of CVD appears to be determined by the circulating concentration of those particles rather than by the mass of cholesterol or triglyceride that they carry (37). This observation, if confirmed, could prove important since 1) significant numbers of youth have elevated non-HDL cholesterol levels, a surrogate marker of apoB, as a result of adverse lifestyles, underlying genetic mutations in TG metabolism, or both; 2) the presence of elevated ApoB during childhood, which often persists into adulthood, represent a much longer period of exposure than that of adult onset; and 3) several novel therapies that potently reduce TG levels are currently in development, some of which have been shown to be effective in youth. However, long-term studies addressing risk reduction and outcomes, safety and FDA approval for use in youth are lacking at this time.

As an alternative to statins, the utility of newer therapies such as ATP citrate lyase inhibitors (ACLY), an enzyme in the cholesterol–biosynthesis pathway upstream of 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR), are being explored. Studies of genetic variants that mimic the effect of ATP citrate lyase inhibitors showed that, compared to statins, ACLY inhibitors appear to lower plasma LDL-C levels by the same mechanism of action. Both were associated with similar effects on the risk of CVD per unit decrease in the LDL-C level (38). These findings, if found to be safe and effective, offer new opportunities for future drug development.

Table 2. Effects on the Risk of CV Events per Decrease of 10 mg/DL in the LDL-C* or ApoB-containing Lipoproteins** Level				
Polygenic Risk Score	**OR**	**95% CI**	**P**	**Reference**
*ACLY score	0.823	0.78 to 0.87	4.0×10−14	Ference, NEJM 2019
*HMGCR score	0.836	0.81 to 0.87	3.9×10−19	Ference, NEJM 2019
**LPL score	0.771	0.741 to 0.802	3.9 × 10−38	Ference, JAMA 2019
**LDLR score	0.773	0.747 to 0.801	1.1 × 10−46	Ference, JAMA 2019

*Mendelian Randomization Study of ACLY and Cardiovascular Disease. Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Kastelein JJP, Nicholls SJ. N Engl J Med. 2019 Mar 14;380(11):1033-1042.

**Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Nicholls SJ, Bhatt DL, Sabatine MS, Catapano ALJAMA. 2019 Jan 29;321(4):364-373

ACQUIRED RISK FACTORS AND RISK CONDITIONS

Risk factors and risk conditions (Table 3) are often acquired during childhood and may accelerate development of ASCVD. In clinical practice dyslipidemia is most commonly encountered in children and adolescents who are obese (BMI $\geq$ 95th percentile) and insulin resistant, the latter clinically manifest by the presence of acanthosis nigricans, impaired or elevated fasting glucose, hypertension, and in girls, polycystic ovarian syndrome (PCOS). There is a striking increase in both severity and extent of atherosclerosis as age and the number of risk factors increases. The presence and intensity of risk factors are highly correlated with the extent and severity of atherosclerosis. Furthermore, risk factors measured in childhood and adolescence have been shown to be better predictors of the severity of atherosclerosis than risk factors measured in young adults (13).

Table 3. Acquired Risk Factors and Risk Conditions

Risk Factors	
Non-Modifiable	**Modifiable**
• Family History • Age • Gender • Perinatal Factors	Nutrition/Diet Physical Inactivity Tobacco Exposure Blood Pressure Lipid Levels Overweight/Obesity Diabetes Mellitus Metabolic Syndrome Inflammation
Risk Conditions	
Moderate Risk	**High Risk**
• Kawasaki disease with regressed coronary aneurysms • Chronic inflammatory diseases • HIV infection	Kawasaki disease with current coronary aneurysms Type 1 and 2 Diabetes Mellitus Post-orthotopic heart transplant

The ability to identify genetic mutations and/or acquired factors or conditions early in this vulnerable population creates the opportunity to prevent development of risk factors and future CVD-related events by effective and timely intervention. All children, including those with genetic dyslipidemia, should be encouraged to follow a heart healthy lifestyle. If begun early, such efforts have the potential of preventing behaviors and risk factors that increase future CVD risk. To assist clinicians in this task, the American Heart Association (AHA) has defined four health behaviors and four health factors that are strongly correlated with ideal cardiovascular health (39). Observational studies of individuals who were able to achieve and maintain one or more ideal cardiovascular health behaviors into middle age had greater longevity, longer morbidity-free survival, compression of morbidity to the end of the lifespan, greater health-related quality of life in older age, and substantially lower healthcare costs later in life (Table 4).

Table 4. Correlation of Health Behaviors and Factors with Ideal Cardiovascular Health

		Number of Health Behaviors* (% lower risk for incidence CHD)				
Study	N	1	2	3	4	5
Males (40)	42,847	(54%)	(63%)	(71%)	(78%)	(87%)
Females (41)	84,129	---	---	(57%)	(66%)	(83%)

Using the seven AHA cardiovascular health metrics, scoring of adolescents using NHANES data showed low scores, especially deficient in points for diet and exercise (42). Retrospective analysis revealed that the seven metrics score in adolescents is inversely associated with cIMT and directly associated with arterial elasticity, suggesting that

this evaluation of cardiovascular wellness can be applied to evaluation of adolescents and targeted as part of primordial prevention (43).

Cardiovascular disease risk factors are associated with both the early and advanced stages of atherosclerosis. Individuals at increased risk should be encouraged to achieve a low lifetime risk by preventing development of risk factors starting in youth. Recognizing that this process begins during childhood is key to facilitating implementation of measures that will prevent atherosclerosis and thereby reduce or eliminate future CVD-related events.

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